IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Van Der Berghe et al.
Serial No.: 10/528,802 Art Unit: 1644
Filed: 23 March 2005

Examiner: Haddad, Maher

Attorney's d ocket: BERGHE 1

Title: Methods and preparations for curing critically ill patients

DECLARATION OF PROFESSOR ALISON FREIFELD, MD, UNDER 37 C.F.R. § 1.132

I, Alison Freifeld, declare and state as follows:

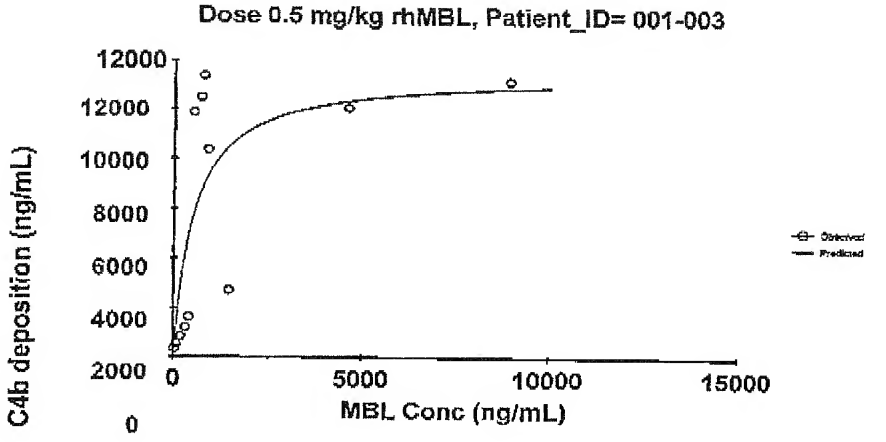
1. I hold an MD degree. I am currently employed as Director of the Immunocompromised Host Infectious Disease Program at the Department of Medicine, University of Nebraska Medical Center, where I am Professor of Medicine.

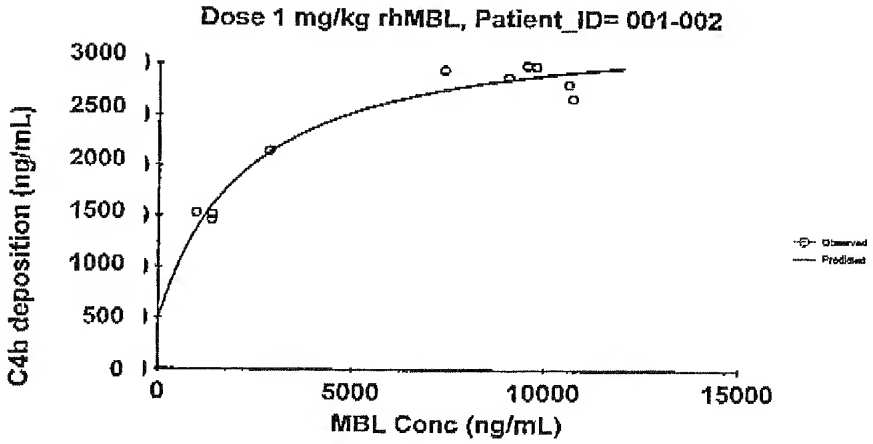
2. I have reviewed and understood the Office Communication of August 23, 2007.

3. The Examiner cites the lack of empirical data and is therefore of the opinion that the specification does not provide enablement for a method comprising a use of MBL for the treatment of a patient in need of transplantation. The Examiner also cites that contradictory activities of MBL have been reported in the art. The data presented herein show that even in solid organ transplant recipients as exemplified by liver transplant recipients, the administration of MBL to these patients increased and normalized complement activity as shown herein by an increased activity in the complement C4b deposition assay.

   Below are provided preliminary results from an ongoing liver transplant study showing the functional pharmacokinetic response of MBL administration. The response is measured as the rise in C4 complement concentration deposited on a plate as a result of the presence of rhMBL.

   - Figure 1 shows that increase in the plasma concentration of MBL leads to an increase in the concentration of complement C4b deposited in vitro on a plate (C4b deposition assay), a test that evaluates complement function. Complement function is measured using the C4b deposition assay. In this assay, MBL in complex with MASP-2 cleaves the complement component C4, thereby leading to deposition of C4by. An increase in the C4b deposition on the plate thus shows that the complement system has been activated, and, in patients with MBL deficiency, has been normalized by rhMBL.


Dose 0.5 mg/kg rhMBL, Patient_ID= 001-003
C4b deposition (ng/mL)
12000
12000
10000
8000
6000
4000
2000
0
0
5000
10000
15000
MBL Conc (ng/mL)
Observed
Predicted


Dose 1 mg/kg rhMBL, Patient_ID= 001-002
C4b deposition (ng/mL)
3000
2500
2000
1500
1000
500
0
0
5000
10000
15000
MBL Conc (ng/mL)
Observed
Predicted

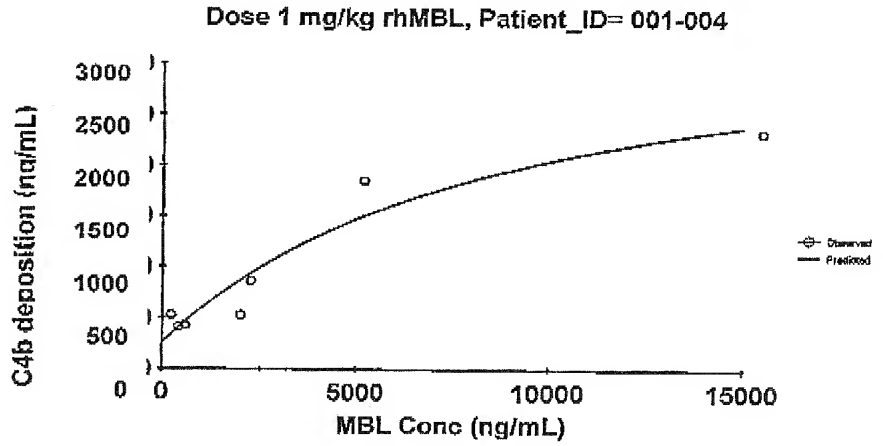
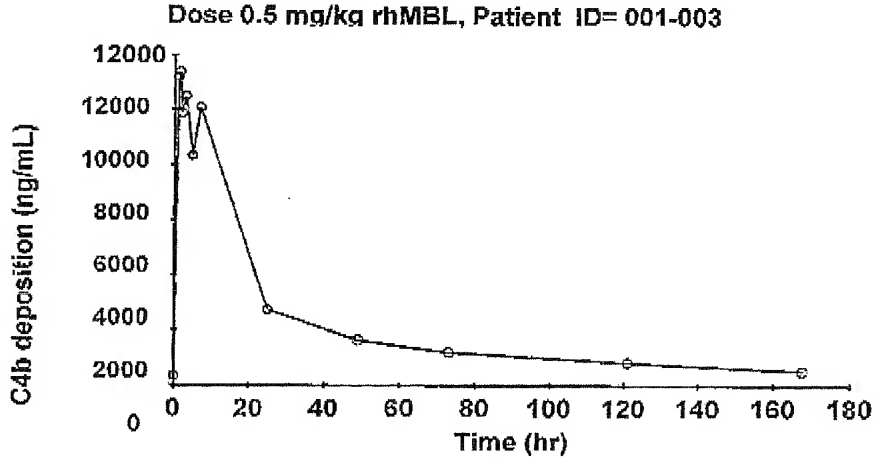
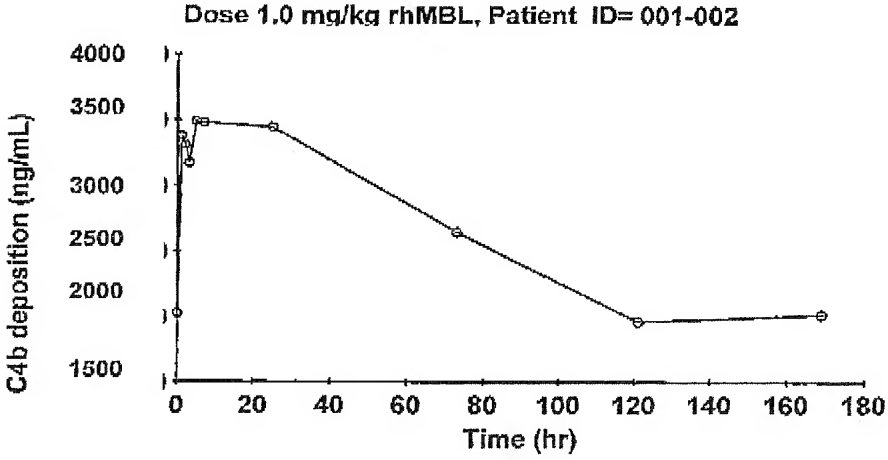

Dose 1 mg/kg rhMBL, Patient_ID= 001-004
C4b deposition (ng/mL)
3000
2500
2000
1500
1000
500
0
0
5000
10000
15000
MBL Conc (ng/mL)
Observed
Predicted

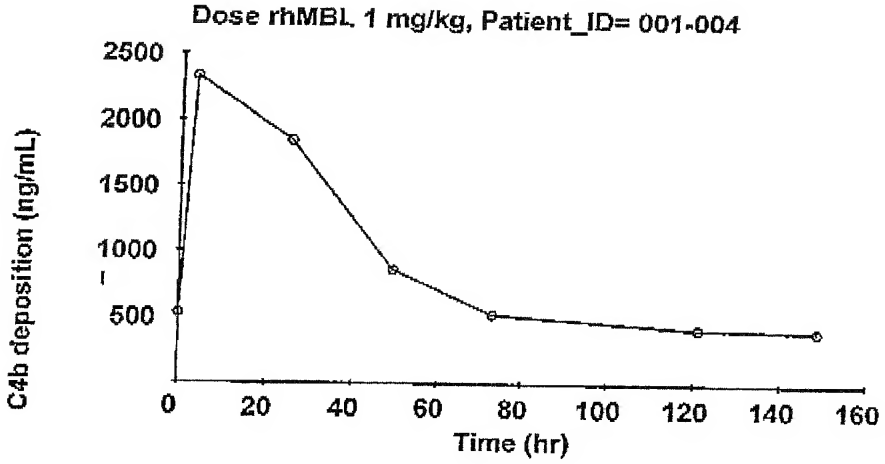
Figure 1 clearly shows that administration of rhMBL to liver transplant recipients increases complement activity as illustrated by an increase in the in vitro assay of complement activity, the C4b deposition assay, with the increase following a classic dose response curve.

Three liver transplant patients received recombinant human MBL (rhMBL) following the transplant. One patient received 0.5 mg/kg rhMBL (patient 001-003) and two patients received 1 mg/kg rhMBL (patients 001-002 and 001-004). The rhMBL was administered by one hour infusion.

Figure 2 shows a time-curve of the functional concentration of rhMBL, as determined by deposition of C4b in vitro, following administration via infusion of 0.5 mg/kg or 1 mg/kg rhMBL..







Liver transplant patients received 0.5 mg/kg rhMBL (patient 001-003) or 1 mg/kg rhMBL (patients 001-002 and 001-004) after transplantation. MBL was administered by one hour infusion.

For all three patients a corresponding rise in the measured C4b deposition activity can be seen following the administration of rhMBL. Following rhMBL administration, the functional activity (C4b deposition activity) decreases with time. The decrease in the C4b deposition activity in the patient receiving 0.5 mg/kg (patient 001-003) is more rapid than the decrease in this functional activity seen for the two patients receiving 1 mg/kg.

The complement system is an important part of the innate immune response and thus important for the protection against infections. A normalized complement system, as shown herein by the increase in the C4b complement deposition assay, is thus indicative of normalization of this important component of the immune system.

Importantly, as of January 16, 2008, administration of rhMBL to liver transplant patients did not result in organ rejection in any of the patients who had received it. The total number of liver transplant patient to whom MBL was administered was 8. The patients have been followed up to 46 weeks post transplant. This demonstrates that administration of MBL to these liver transplant patients was safe thus far.

4. The results described herein demonstrate convincingly that rhMBL administration normalizes C4b complement deposition activity in vitro and that normalization of complement activation correlates with rhMBL levels. These Experiments thus show the biologic efficacy of MBL administration even in solid organ transplant recipients. In addition, administration of MBL to liver transplant patients did not result in organ rejection in any of the 8 patients who have received it thus far and who have been followed up to 46 weeks post transplant.

5. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 21 January 2008 Signature: Alison Freifeld MD

(Alison Freifeld MD)